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09/203,500	12/01/98	HONOLD K	P564-8025

EXAMINER	
SANDALS,W	
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DATE MAILED: 02/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/203,500	Applicant(s) Honold et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Nov 17, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *20-43* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *20-43* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *17*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Arguments set forth in Paper No. 19, filed November 17, 2000 have been considered and found convincing. Arguments set forth in Paper No. 19 assert that the rejections "mischaracterized" the claimed invention, and as a result the rejections did not address the true nature of the claimed invention. New grounds of rejection, and newly cited prior art are presented in the new rejections below to address these arguments. The previous rejections under 35 USC 103 are withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 20-25, 28-32, 35 and 37-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 20 recites the limitation "the sequences" in lines 8 and 9. There is insufficient antecedent basis for this limitation in the claim.

5. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

§ 2172.01. The omitted steps are: There is no step which connects the expression of the heterologous control sequence of step (a) with the expression of the endogenous gene of step (d). Merely reciting "conditions under which" does not tell one of skill in the art what means may be involved which links the expression of the heterologous sequence to the expression of the endogenous sequence.

6. Claim 23 recites the limitation "the sequences" in line 2. There is insufficient antecedent basis for this limitation in the claim.

7. Claim 24 recites the limitation "the sequences" in lines 6 and 7. There is insufficient antecedent basis for this limitation in the claim.

8. Claim 25 recites the limitation "the sequences" in line 5. There is insufficient antecedent basis for this limitation in the claim.

9. Claim 28 recites the limitation "the sequences" in line 6. There is insufficient antecedent basis for this limitation in the claim.

10. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: There is no step which connects the expression of the sequence which binds an activator protein of step (a) with the expression of the endogenous gene of step (d). Merely reciting "conditions under which" does not tell one of skill in the art what means may be involved which links the expression of the sequence which binds an activator protein to the expression of the endogenous sequence.

11. Claim 32 recites the limitation "the sequences" in line 4. There is insufficient antecedent basis for this limitation in the claim.

12. Claim 35 recites the limitation "the expression control sequence" in lines 9-10. There is insufficient antecedent basis for this limitation in the claim.

13. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: There is no step which connects the expression of the non-coding sequence of step (a) with the expression of the target gene of step (c). Merely reciting "conditions under which" does not tell one of skill in the art what means may be involved which links the expression of the non-coding sequence to the expression of the target sequence.

14. Claim 35 recites the limitation "the expression" in lines 11 and 12. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: There is no step which provides for a means of producing a DHFR-negative mammalian cell. Homologous recombination of the vector into a cell does not provide a clear understanding of the process of inactivation of a DHFR gene. Further, there is no provision for a DHFR gene in the target cell.

16. Claim 37 recites the limitation "the sequences" in lines 10 and 13. There is insufficient antecedent basis for this limitation in the claim.

17. Claim 39 recites the limitation "the sequences" in line 6. There is insufficient antecedent basis for this limitation in the claim.

18. Claim 40 recites the limitation "the sequences" in lines 3 and 5. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

20. Claims 25-27, 32-35 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 5,695,977.

US Pat No. 5,695,977 taught (see especially the abstract and columns 2-8) a vector comprising an amplification gene sequence (DHFR), or a nucleic acid which binds an activator protein, and a selectable marker flanked by recombinase target sequences which may have a negative selection marker outside the recombinase target sequences. The vector may be inserted adjacent to an endogenous gene. The vector may be present in a human cell. Also taught is a process for testing the action of the amplification gene sequence or a nucleic acid which binds an activator protein on the expression of an endogenous target gene.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 36-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,020,144 in view of Cruz et al. (PNAS, Vol. 88, 1991).

The claims are drawn to a process for obtaining a DHFR-negative mammalian cell by transfecting the cell with a first vector comprising at least one target sequence for a site-specific recombinase, homologous DHFR DNA sequences which flank the recombinase site-specific sequence(s) and an optional positive selection marker gene and an optional negative selection marker gene. Transfecting the vector in the cell whereby homologous recombination occurs causing the vector to insert in the genome of the cell to produce a DHFR-negative cell. The claims are also drawn to a process for producing a mammalian cell which has been transfected with a vector which introduced a heterologous DHFR gene into the genome of the DHFR-negative cell by homologous recombination.

US Pat No. 6,020,144 taught (see especially columns 5, 15 and example 2) a process for obtaining a DHFR-negative trypanosomal cell by transfecting the cell with a first vector comprising at least one target sequence for a site-specific recombinase, homologous DHFR DNA sequences which flank the recombinase site-specific sequence(s) and an optional positive

selection marker gene and an optional negative selection marker gene. Transfecting the vector in the cell whereby homologous recombination occurs causing the vector to insert in the genome of the cell to produce a DHFR-negative trypanosomal eukaryotic cell. US Pat No. 6,020,144 also taught a process for producing a trypanosomal cell which has been transfected with a vector which introduced a heterologous DHFR gene into the genome of the DHFR-negative cell by homologous recombination.

US Pat No. 6,020,144 did not teach that the cell was a mammalian cell.

Cruz et al. taught (see especially the abstract) the deletion of DHFR and subsequent replacement with a heterologous DHFR in a cell. Cruz et al. taught that the cell may be a mammalian cell.

It would have been obvious to one of skill in the art at the time of filing the instant application to combine a process for obtaining a DHFR-negative mammalian cell by transfecting the cell with a first vector comprising at least one target sequence for a site-specific recombinase, homologous DHFR DNA sequences which flank the recombinase site-specific sequence(s) and an optional positive selection marker gene and an optional negative selection marker gene, then transfecting the vector in the cell whereby homologous recombination occurs causing the vector to insert in the genome of the cell to produce a DHFR-negative trypanosomal eukaryotic cell. Also taught was a process for producing a trypanosomal cell which has been transfected with a vector which introduced a heterologous DHFR gene into the genome of the DHFR-negative cell by homologous recombination of US Pat No. 6,020,144 with the process of deletion of DHFR

and subsequent replacement with a heterologous DHFR in a cell where the cell may be a mammalian cell as taught by Cruz et al. because both US Pat No. 6,020,144 and Cruz et al. were investigating the replacement of DHFR in a trypanosomal cell with a heterologous DHFR. Cruz et al. taught that the process may be practiced in a mammalian cell.

One of skill in the art would have been motivated at the time of filing the instant application to combine a process for obtaining a DHFR-negative mammalian cell by transfecting the cell with a first vector comprising at least one target sequence for a site-specific recombinase, homologous DHFR DNA sequences which flank the recombinase site-specific sequence(s) and an optional positive selection marker gene and an optional negative selection marker gene, then transfecting the vector in the cell whereby homologous recombination occurs causing the vector to insert in the genome of the cell to produce a DHFR-negative trypanosomal eukaryotic cell. Also taught was a process for producing a trypanosomal cell which has been transfected with a vector which introduced a heterologous DHFR gene into the genome of the DHFR-negative cell by homologous recombination of US Pat No. 6,020,144 with the process of deletion of DHFR and subsequent replacement with a heterologous DHFR in a cell where the cell may be a mammalian cell as taught by Cruz et al. because both US Pat No. 6,020,144 and Cruz et al. were investigating the replacement of DHFR in a trypanosomal cell with a heterologous DHFR. Cruz et al. taught in the abstract "[t]he double targeting replacement method will enable functional genetic testing in a variety of asexual diploids, including cultured mammalian cells". Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the

producing the instant claimed invention given the teachings of US Pat No. 6,020,144 and Cruz et al.

23. Claims 20-28 and 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,695,977 in view of WO 94/12650 and US Pat No. 6,130,364.

The claims are drawn to the invention as described in the rejection above, and where the vector comprises at least one nucleic acid which binds an activator protein.

US Pat No. 5,965,977 taught the invention as described above.

US Pat No. 5,695,977 did not teach a vector which comprises at least one nucleic acid which binds an activator protein which is a heterologous control sequence.

US Pat No. 6,130,364 taught (see especially the abstract and columns 11-12, 13,16-17 and 21) a process for introducing a vector by homologous recombination adjacent to a target gene, where the vector comprised at least one nucleic acid which binds an activator protein which is a heterologous control sequence which is flanked by recombinase target sites which is in turn flanked by sequences which target the vector to insert by homologous recombination at a site adjacent to a target gene.

WO 94/12650 taught (see especially the abstract and pages 2-5 and 16-23 and example 6) a process for introducing a vector by homologous recombination adjacent to a target gene, where the vector comprised at least one nucleic acid which binds an activator protein which is a heterologous control sequence which is flanked by recombinase target sites which is in turn

flanked by sequences which target the vector to insert by homologous recombination at a site adjacent to a target gene.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the vector comprising an amplification gene sequence (DHFR), or a nucleic acid which binds an activator protein, and a selectable marker flanked by recombinase target sequences which may have a negative selection marker outside the recombinase target sequences. The vector may be inserted adjacent to an endogenous gene. The vector may be present in a human cell. Also taught is a process for testing the action of the amplification gene sequence or a nucleic acid which binds an activator protein on the expression of an endogenous target gene as taught by US Pat No. 5,695,977 with the process for introducing a vector by homologous recombination adjacent to a target gene, where the vector comprised at least one nucleic acid which binds an activator protein which is a heterologous control sequence which is flanked by recombinase target sites which is in turn flanked by sequences which target the vector to insert by homologous recombination at a site adjacent to a target gene of WO 94/12650 and US Pat No. 6,130,364 because the nucleic acid which binds an activator protein and the amplification sequence are both taught as equivalents by WO 94/12650.

One of ordinary skill in the art would have been motivated at the time of filing of the instant application to combine the vector comprising an amplification gene sequence (DHFR), or a nucleic acid which binds an activator protein, and a selectable marker flanked by recombinase target sequences which may have a negative selection marker outside the recombinase target

sequences. The vector may be inserted adjacent to an endogenous gene. The vector may be present in a human cell. Also taught is a process for testing the action of the amplification gene sequence or a nucleic acid which binds an activator protein on the expression of an endogenous target gene as taught by US Pat No. 5,695,977 with the process for introducing a vector by homologous recombination adjacent to a target gene, where the vector comprised at least one nucleic acid which binds an activator protein which is a heterologous control sequence which is flanked by recombinase target sites which is in turn flanked by sequences which target the vector to insert by homologous recombination at a site adjacent to a target gene of WO 94/12650 and US Pat No. 6,130,364 because WO 94/12650 taught at page 22, line 29 bridging to page 23, line 2 "targeting sequences - DNA encoding an amplifiable positively selectable marker - DNA encoding a second selectable marker (optional) - DNA sequences corresponding to either an exogenous gene to be expressed under the control of a suitable promoter or a promoter only which is positioned to activate an endogenous gene - targeting DNA sequences." Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of US Pat No. 5,695,977 with WO 94/12650 and US Pat No. 6,130,364.

24. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,695,977 in view of WO 94/12650 and US Pat No. 6,130,364 as applied to claims 20-28 and 30-35 above, and further in view of WO 97/37012.

The claims are drawn to the invention as described above and to hypoxia-inducible factor-binding nucleic acid sequence.

5,695,977 in view of WO 94/12650 and US Pat No. 6,130,364 taught the invention as described above.

5,695,977 in view of WO 94/12650 and US Pat No. 6,130,364 did not teach that the vector comprised at least one nucleic acid which binds an activator protein which was a hypoxia-inducible factor-binding nucleic acid sequence.

WO 97/37012 taught (see especially pages 11-12) a vector which introduced control sequences adjacent to a target gene by homologous recombination where the control sequence was a hypoxia-inducible factor-binding nucleic acid sequence.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the invention of US Pat No. 5,695,977 in view of WO 94/12650 and US Pat No. 6,130,364 as described above with the vector which comprised at least one nucleic acid which binds an activator protein which was a hypoxia-inducible factor-binding nucleic acid sequence of WO 97/37012 because WO 97/37012 taught the equivalence of the vector which comprised at least one nucleic acid which binds an activator protein of US Pat No. 5,695,977 in view of WO 94/12650 and US Pat No. 6,130,364 with a vector which comprised at least one nucleic acid which binds an activator protein which was a hypoxia-inducible factor-binding nucleic acid sequence.

One of ordinary skill in the art would have been motivated at the time of filing of the instant application to combine the invention of US Pat No. 5,695,977 in view of WO 94/12650 and US Pat No. 6,130,364 as described above with the vector which comprised at least one nucleic acid which binds an activator protein which was a hypoxia-inducible factor-binding nucleic acid sequence of WO 97/37012 because WO 97/37012 taught at page 11, line 22 bridging to page 12, line 5 "[e]xamples of preferred promoters....heat shock or other environmentally-inducible promoter such as those induced by anaerobiosis or hypoxia". Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of US Pat No. 5,695,977 in view of WO 94/12650 and US Pat No. 6,130,364, and further in view of WO 97/37012.

Conclusion

25. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz can be reached at (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.

Examiner

January 30, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER